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Abstract

Medication vehicles have particles made of lipids, lipid-like (lipoid) materials or mixtures thereof, with a diameter from 10 nm to 10 mu m, that are solid at the ambient temperature. Because or their solid core, these medication vehicles allow active substances to be controllably released over a longer period, allow hydrophilic medicaments to be incorporated into the solid core and are relatively quickly decomposable, producing no toxic by-products.

die intravenöse Gabe, intramuskuläre Gabe, intraartrikoläre Gabe, intracavitale Gabe, subkutane Gabe, intradermale Gabe, enterale Gabe, pulmonale Applikation sowie topische und ophtalmologische Anwendung geeignet sind.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE

1. Process for the manufacture of a drug carrier which comprises tensidecontaining or tenside-free particles of lipid or lipid-like (lipoid) material, or mixtures thereof, which have a diameter of 10 nm to 10 µm, whereby the particles of the main population have an average diameter of between 40 and 1000 nm and are solid at room temperature, characterised by the fact that either the inner phase (the lipid or lipoid) is homogenised under high pressure in the dispersion medium (water, aqueous solution or a liquid which can be mixed with water) in a melted or softened state, whereby, where melted lipid or lipoid is used as the inner phase during homogenisation under high pressure, one or more active substances are also present and are encapsulated in the lipid or lipoid, or the inner phase is dispersed under high pressure in the dispersion medium in a solid state, whereby the solid phase is finely broken down.

2. Process for the manufacture of a drug carrier which comprises tensidecontaining or tenside-free particles of lipid or lipid-like (lipoid) material, or mixtures thereof, which have a diameter of 10 nm to 10 µm, whereby the particles of the main population have an average diameter of between 40 and 1000 nm and are solid at room temperature, characterised by the fact that either the inner phase (the lipid or lipoid) is homogenised under high pressure in the dispersion medium (water, aqueous solution or a liquid which can be mixed with water) in a melted or softened state, or the inner phase is dispersed under high pressure in the dispersion medium in a solid state, whereby the solid phase is finely broken down, and the drug carrier includes one or more active substances which are selected from:

Analgesics/antirheumatics selected from
morphine, codeine, piritamide, fentanyl and fentanyl derivatives, levomethadone, tramadol, diclofenac, ibuprofen, naproxen, piroxicam, penicillamine;
Antiallergics;
Antibiotics/chemotherapeutics selected from
polypeptide antibiotics; anti-malaria drugs, the virunstatics ganciclovir, foscarnet, zidovudine, aciclovir and dapsone, fosfomycin, fusafungine, trimethoprim;
Antiepileptics;
Antimycotics selected from
nystatin, natamycin, amphotericin B, flucytosine, miconazole, fluconazole, itraconazole, clotrimazole, econazole, tioconazole, fenticonazole, bifonasole, ketoconzole, isoconazole, tolnaftate;
Corticosteroids selected from
aldosterone, fludrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, prednylidene, cloprednol, methylprednisolone;
Dermatological drugs selected from

a) the antibiotics tetracycline, erythromycin, neomycin, gentamycin, clindamycin, framycetin, tyrothricin, chlorotetracycline, mipirocin, fusidinic acid
b) the virustatics podophyllotoxin, vidarabine, tromantadine,
c) the corticosteroids amcinodid, fluprednidene, aldometasone, clobetasol, diflorasone, halcinonid, fluocinolone, clocortolone, flumetasone, diflucortolone, fludroxycortid, halomethasone, desoxymethasone, fluocinolide, fluocortinbutyl, fluprednidene, prednicarbate, desonid;

Diagnostics;
Haemostyptics/antihaemorragics;
Hypnotics, sedatives; Hypophysis and hypothalmus hormones, regulatory peptides and their inhibitors;
Immune therapeutics and cytokines;
Local anaesthetics;
Migraine treatments;
Narcotics;

Parathyroid hormones, calcium metabolism regulators;
Opthalmics;
Psychopharmaceutics;
Thyroid drugs;
Serums, immunoglobulins, vaccines;
Sexual hormones and their inhibitors;
Cystostatics and metastasis inhibitors.

3. Process as in claim 1 or 2, characterised by the fact that the particles of the main population have an average diameter of 100 to 500 nm and, with appropriate selection of process parameters and auxiliary media, have an average diameter of 40 to 80 nm.

4. Process as in claim 1, 2 or 3, characterised by the fact that the proportion of the inner or lipid phase in relation to the basic preparation is 0.1 to 30 % by weight and, especially, 1 to 10 % by weight.

5. Process as in one of the claims 1 to 4, characterised by the fact that the particle material comprises monoglyceride, diglyceride and triglyceride, fatty alcohols and the esters or ethers thereof, waxes and lipid peptides or mixtures of these.

6. Process as in one of the claims 1 to 5, characterised by the fact that the triglyceride comprises glycerine trilaurate, glycerine myristate, glycerine palmitate, glycerine stearate and glycerine behenate, that the fatty alcohol comprises cetyl and stearyl alcohol and the wax comprises cetyl palmitate and bleached beeswax.

7. Process as in one of the claims 1 to 6, characterised by the fact that, in addition, the drug carrier includes one or more dispersionstabilising substances, whereby the dispersion-stabilising substances are included in a quantity of 0.01 to 20 % by weight in relation to the basic preparation, ideally 0.5 to 5 % by weight.

8. Process as in claim 7, characterised by the fact that the stabilising substances comprise compounds from the series of poloxamers, poloxamins, ethoxylated monoglycerides and diglycerides, ethoxylated lipids and lipoids, ethoxylated fatty alcohols and alkyl phenols, ethoxylated fatty acid esters, polyglycerine ethers and esters, lecithins, esters and ethers of sugars or sugar alcohols with fatty acids and fatty alcohols, phospholipids and sphingolipids, sterols or the esters and ethers thereof, as well as mixtures of these compounds.

9. Process as in claim 7 or 8, characterised by the fact that the stabilising substance comprises egg-lecithin, soya-lecithin or hydrogenated lecithin, mixtures thereof, or mixtures of one or both lecithins with one or more phospholipid components, cholesterin, cholesterin palmitate, stigmaterin or other sterols.

10. Process as in one of the preceding claims, characterised by the fact that, in addition, the drug carrier includes load stabilisers in a quantity of 0.1 to 10 % by weight and especially 0.05 to 2 % by weight in relation to the basic preparation.

11. Process as in claim 10, characterised by the fact that the load stabilisers comprise dicetyl phosphate, phosphatidylglycerol, saturated or unsaturated fatty acids, sodium cholate, sodium glycocholate, sodium taurocholate or mixtures thereof, peptisators or amino acids.

12. Process as in claim 7, characterised by the fact that the drug carrier comprises one or more viscosity-increasing substances, whereby the viscosity-increasing substances are included in a quantity of 0.1 to 10 % by weight in particular, ideally 0.5 to 5 % by weight, in relation to the basic preparation.

13. Process as in claim 12, characterised by the fact that the viscosityincreasing substances comprise cellulose ethers and esters, polyvinyl derivatives, alginates, polyacrylates, xanthanes and pectins.

14. Process as in claim 12 or 13, characterised by the fact that the drug carrier also comprises sugar or sugar alcohols, especially glucose, mannose, trehalose, mannitol and sorbitol.

15. Process as in one of the claims 12 to 14, characterised by the fact that the drug carrier also comprises load carriers.

16. Process as in one of the preceding claims, characterised by the fact that the particles are dispersed in distilled

water, in an aqueous solution with additives of electrolytes, monosaccharides and disaccharides, polyols or mixtures thereof or a liquid that can be mixed with water, whereby the additives comprise, in particular, sodium chloride, mannose, glucose, fructose, xylose, trehalose, mannitol, sorbitol, xylitol and glycerol, preferably in a quantity of 0.1 to 50 % by weight and especially 1 to 30 % by weight in relation to the basic preparation.

17. Process as in one of the preceding claims, characterised by the fact that the particles are lyophilised or spray-dried.

18. Process as in claim 1 or 2, characterised by the fact that the drug carrier is manufactured without the use of halogenated organic solvents.

19. Process as in one of the preceding claims, characterised by the fact that the drug carrier includes one or more active substances.

20. Process as in claim 19, characterised by the fact that the active substance or substances are dissolved or dispersed in the particles or dispersed in the particles as an aqueous solution.

21. Process as in claim 19, characterised by the fact that the drug carrier contains one or more active substances and is suitable for intravenous administration, intramuscular administration, intra-arthricular administration, intracavital administration, subcutaneous administration, intradermal administration, enteral administration, pulmonary application and topical and opthalmological application.

22. Drug carrier consisting of tenside-free particles of lipid or lipidlike (lipoid) material, or mixtures thereof, with a diameter of 10 nm to 10 µm, which can be manufactured by means of a high-pressure homogenisation process in accordance with one of the claims 1 to 20, whereby the particles of the main population have an average diameter of between 40 and 1000 nm and are solid at room temperature, excluding such carriers where the active substance or substances are only adsorbed onto the surface of the solid inner phase following dispersion under high pressure of the inner phase, in a finely broken-down state, in the dispersion medium.

23. Use of a drug carrier as in claim 22 for the manufacture of drugs which are, in particular, suitable for intravenous administration, intramuscular administration, intra-arthricular administration, intracavital administration, subcutaneous administration, intradermal administration, enteral administration, pulmonary application and topical and opthalmological application.

Claims for the following Contracting State : IE

1. Process for the manufacture of a drug carrier which comprises tenside-containing or tensid-free particles of lipid or lipid-like (lipoid) material, or mixtures thereof, which have a diameter of 10 nm to 10 µm, whereby the particles of the main population have an average diameter of between 40 and 1000 nm and are solid at room temperature, characterised by the fact that either the inner phase (the lipid or lipoid), is homogenised under high pressure in the dispersion medium (water, aqueous solution or a liquid which can be mixed with water) in a melted or softened state, or the inner phase is dispersed under high pressure in the dispersion medium in a solid state, whereby the solid phase is finely broken down.

2. Process as in claim 1, characterised by the fact that the particles of the main population have an averaged diameter of 100 to 500 nm and, with appropriate selection of process parameters and auxiliary media, have an average diameter of 40 to 80 nm.

3. Process as in claim 1 or 2, characterised by the fact that the proportion of the inner or lipid phase in relation to the basic preparation is 0.1 to 30 % by weight and, especially, 1 to 10 % by weight.

4. Process as in one of the claims 1 to 3, characterised by the fact that the particle material comprises monoglyceride, diglyceride. triglyceride, fatty alcohols and the esters or ethers thereof, waxes and lipid peptides or mixtures of these.

5. Process as in one of the claims 1 to 4, characterised by the fact that the triglyceride comprises glycerine trilaurate, glycerine myristate, glycerine palmitate, glycerine stearate and glycerine behenate, that the fatty alcohol comprises cetyl and stearyl alcohol and the wax comprises cetyl palmitate and bleached beeswax.

6. Process as in one of the claims 1 to 5, characterised by the fact that, in addition, the drug carrier includes one or more dispersion-stabilising substances, whereby the dispersion-stabilising substances are included in a quantity of 0.1 to 20 % by weight in relation to the basic preparation, ideally 0.5 to 5 % by weight.

7. Process as in claim 6, characterised by the fact that the stabilising substances comprise compounds from the series of poloxamers, poloxamins, ethorylated monoglycerides and diglycerides, ethorylated lipids and lipoids, ethoxylated fatty alcohols and alkyl phenols, ethoxylated fatty acid esters, polyglycerine ethers and esters, lecithins, esters and ethers of sugars or sugar alcohols with fatty acids or fatty alcohols, phospholipids and sphingolipids, sterols or the esters and ethers thereof, as well as mixtures of these compounds.

8. Process as in claim 6 or 7, characterised by the fact that the stabilising substance comprises egg-lecithin, soya-lecithin or hydrogenated lecithin, mixtures thereof, or mixtures of one or both lecithins with one or more phospholipid components, cholesterin, cholesterin palmitate, stigmaterin or other sterols.

9. Process as in one of the preceding claims, characterised by the fact that, in addition, the drug carrier includes load stabilisers in a quantity of 0.01 to 10 % by weight and especially 0.05 to 2 % by weight.

10. Process as in claim 9, characterised by the fact that the load stabilisers comprise dicetyl phosphate, phosphatidylglycerol saturated or unsaturated fatty acids, sodium cholate, sodium glycocholate, sodium taurocholate or mixtures thereof, peptisators or amino acids.

11. Process as in claim 6, characterised by the fact that the drug carrier comprises one or more viscosity-increasing substances, whereby the viscosity-increasing substances are included in a quantity of 0.1 to 10 % by weight, ideally 0.5 to 5 % by weight in relation to the basic preparation.

12. Process as in claim 11, characterised by the fact that the viscosity-increasing substances comprise cellulose ethers and esters, polyvinyl derivatives, alginates, polyacrylates, xanthanes and pectins.

13. Process as in claim 11 or 12, characterised by the fact that the drug carrier also comprises sugar or sugar alcohols, especially glucose, mannose, trehalose, mannitol and sorbitol.

14. Process as in one of the claims 11 to 13, characterised by the fact that the drug carrier also comprises load carriers.

15. Process as in one of the preceding claims, characterised by the fact that the particles are dispersed in distilled water, in an aqueous solution with additives of electrolytes, monosaccharides and disaccharides, polyols or mixtures thereof or a liquid that can be mixed with water, whereby the additives comprise, in particular, sodium chloride, mannose, glucose, fructose, xylose, trehalose, mannitol, sorbitol, xylitol and glycerol, preferably in a quantity of 0.1 to 50 % by weight and especially 1 to 30 % by weight in relation to the basic preparation.

16. Process as in one of the preceding claims, characterised by the fact that the particles are lyophilised or spray-dried.

17. Process as in claim 1, characterised by the fact that the drug carrier is manufactured without the use of halogenated organic solvents.

18. Process as in one of the preceding claims, characterised by the fact that the drug carrier includes no active substance, or one or more active substances.

19. Process as in claim 18, characterised by the fact that the active substance or substances are dissolved or dispersed in the particles, adsorbed on the surface of the particles or dispersed in the particles as an aqueous solution.

20. Process as in claim 18, characterised by the fact that the drug carrier contains one or more active substances and is suitable for intravenous administration, intramuscular administration, intra-arthricular administration, intracavital administration, subcutaneous administration, intradermal administration, enteral administration, pulmonary application and topical and opthalmological application.

21. Drug carrier consisting of tensid-free particles of lipid or lipid-like (lipoid) material, or mixtures thereof, with a diameter of 10 nm to 10 nμ, which can be manufactured by means of a high-pressure homogenisation process in

accordance with one of the claims 1 to 19, whereby the particles of the main population have an average diameter of between 40 and 1000 nm and are solid at room temperature.

22. Use of a drug carrier as in claim 21 for the manufacture of drugs which are, in particular, suitable for intravenous administration, intramuscular administration, intra-arthricular administration, intracavital administration, subcutaneous administration, intradermal administration, enteral administration, pulmonary application and topical and opthalmological application.

Revendications

Revendications pour les Etats contracts suivants : AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE

1. Procédé pour la préparation d'un véhicule de substance médicamenteuse, qui comprend des particules contenant un tensioactif ou exemptes de tensioactif, à base de lipide, d'une substance de type lipidique (lipoïdique) ou de mélanges de ceux-ci, qui présentent un diamètre de 10 nm à 10 µm, la majeure partie des particules ayant un diamètre moyen compris entre 10 et 1 000 nm, et étant solides à la température ambiante, caractérisé en ce que soit la phase interne (le lipide ou lipoïde) est homogénéisée sous haute pression, à l'état fondu ou ramolli, dans le milieu de mise en dispersion (eau, solution aqueuse ou liquide miscible à l'eau) étant entendu que lors de l'utilisation du lipide ou lipoïde fondu en tant que phase interne pendant l'homogénéisation sous haute pression, une ou plusieurs substances actives sont également présentes et incorporées au lipide ou lipoïde, soit la phase interne est dispersée sous haute pression, à l'état solide, la phase solide étant finement divisée, dans le milieu de mise en dispersion.

2. Procédé pour la préparation d'un véhicule de substance médicamenteuse, qui comprend des particules contenant un tensioactif ou exemptes de tensioactif, à base de lipide, d'une substance de type lipidique (lipoïdique) ou de mélanges de ceux-ci, qui présentent un diamètre de 10 nm à 10 µm, la majeure partie des particules ayant un diamètre moyen compris entre 40 et 1 000 nm, et étant solides à la température ambiante, caractérisé en ce que soit la phase interne (le lipide ou lipoïde) est homogénéisée sous haute pression, à l'état fondu ou ramolli, dans le milieu de mise en dispersion (eau, solution aqueuse ou liquide miscible à l'eau), soit la phase interne est dispersée sous haute pression, à l'état solide, la phase solide étant finement divisée, dans le milieu de mise en dispersion, et le véhicule de substance médicamenteuse comprend une ou plusieurs substances actives, qui sont choisies parmi :

Analgésiques/antirhumatismaux choisis parmi :
morphine, codéine, piritamide, fentanyle et dérivés de fentanyle, lévométhadone, tramadole, diclofénac, ibuprofène, naproxène, piroxicam, pénicillamine;
Antiallergiques;
Antibiotiques/agents chimiothérapeutiques choisis parmi:
antibiotiques polypeptidiques, agents antipaludéens, l'antiviral ganciclovir, le foscarnet, la zidovudine, l'aciclovir et la dapsone, la fosfomycine, la fusafungine, le triméthoprime;
Antiépileptiques;
Antifongiques choisis parmi :
nystatine, natamycine, amphotéricine B, flucytosine, miconazole, fluconazole, itraxonazole, clotrimazole, éconazole, tioconazole, fenticonazole, bifonazole, kétoconazole, isoconazole, tolnaftate;
Corticoïdes choisis parmi :
aldostérone, fluodrocortisone, bétaméthasone, dexaméthasone, fluocortolone, prednisolone, prednylidène, cloprednole, méthylprednisolone.

Produits dermatologiques choisis parmi :

a) les antibiotiques tétracycline, érythromycine, néomycine, gantamycine, clindamycine, framycétine, tyrothricine, chlorotétracycline, mipirocine, acide fusidique;
b) les antiviraux podophyllotoxine, vidarabine, tromantadine;
c) les corticoïdes amcinonide, fluprednidène, alcométhasone, clobétasole, diflorasone, halcinonide, fluocinolone, clocortolone, fluméthasone, difluocortolone, fludroxycortide, halométhasone, désoximéthasone, fluocinolide, fluocortinbutyle, fluprednidène, prednicarbate, désonide;

Produits diagnostiques;